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(21) International Application Number: PCT/US99/09610 (22) International Filing Date: 30 April 1999 (30.04.99) (30) Priority Data: <table border="0"><tr><td>09/071,457</td><td>1 May 1998 (01.05.98)</td><td>US</td></tr><tr><td>09/166,703</td><td>5 October 1998 (05.10.98)</td><td>US</td></tr><tr><td>09/175,395</td><td>19 October 1998 (19.10.98)</td><td>US</td></tr><tr><td>09/260,099</td><td>2 March 1999 (02.03.99)</td><td>US</td></tr><tr><td>09/262,715</td><td>4 March 1999 (04.03.99)</td><td>US</td></tr></table> (71) Applicant: RT ALAMO VENTURES, INC. [US/US]; 10464 Sunset Boulevard, Los Angeles, CA 90077 (US). (74) Agents: CARROLL, Peter, G. et al.; Medlen & Carroll, LLP, Suite 2200, 220 Montgomery Street, San Francisco, CA 94104 (US).		09/071,457	1 May 1998 (01.05.98)	US	09/166,703	5 October 1998 (05.10.98)	US	09/175,395	19 October 1998 (19.10.98)	US	09/260,099	2 March 1999 (02.03.99)	US	09/262,715	4 March 1999 (04.03.99)	US	(81) Designated States: AU, CA, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
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(54) Title: THE TREATMENT OF SEXUAL DYSFUNCTION IN CERTAIN PATIENT GROUPS (57) Abstract <p>Methods for treating specific patient groups for sexual dysfunction are provided. The methods of the present invention comprise the utilization of pharmaceutical compositions in patients who are free of cardiac disease and/or who have not been given organic nitrates.</p>																	

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THE TREATMENT OF SEXUAL DYSFUNCTION IN CERTAIN PATIENT GROUPS

FIELD OF THE INVENTION

5 The present invention provides relates to methods for the treatment of sexual dysfunction in males and females (including but not limited to erectile dysfunction in males) in particular treatment groups. The methods of the present invention comprise the utilization of pharmaceutical compositions to patients who are free of symptoms of cardiac disease and who have not been treated with drugs which cause hypotensive effects, such as nitrites and nitrates.

10 BACKGROUND

Impotence or erectile insufficiency is a widespread disorder that is thought to affect about twelve percent of adult men under age forty-five, about twenty percent of men at age sixty, and about fifty-five percent of men at age seventy-five.

15 There is more than one cause of erectile dysfunction. For example, erectile dysfunction can be psychological, resulting from anxiety or depression, with no apparent somatic or organic impairment. Such erectile dysfunction, which is referred to as "psychogenic", is responsible for about fifteen to twenty percent of cases of impotence. In other cases, the erectile dysfunction is associated with atherosclerosis of the arteries supplying blood to the penis; such dysfunction is referred to as
20 "arteriogenic" or "atherosclerotic." About forty to sixty percent of cases of impotence are arteriogenic in origin.

In still other cases, there is leakage from veins in the penis such that sufficient pressure for an erection can be neither obtained nor maintained. This dysfunction is referred to as "venous leakage," or "abnormal drainage". This condition is often
25 exacerbated by the presence of some arteriogenic dysfunction whereby the supply of blood to the penis is impaired. In still other cases, the dysfunction is associated with a neuropathy, such as nerve damage arising from, for example, surgery or a pelvic

injury, in the nervous system affecting the penis. Such a dysfunction is referred to as "neurogenic" and this accounts for about ten to fifteen percent of cases of impotence.

There is also a high incidence of erectile insufficiency among diabetics, particularly those with insulin-dependent diabetes mellitus. Erectile dysfunction in diabetics is often classified as "diabetogenic," although the underlying dysfunction is usually neurogenic associated with neuropathy, but may be arteriogenic or neurogenic and arteriogenic. About half of diabetic males suffer from erectile insufficiency, and about half of the cases of neurogenic impotence are in diabetics.

Additionally, erectile insufficiency is sometimes a side effect of certain drugs, such as beta-blockers that are administered to reduce blood pressure in persons suffering from hypertension, or drugs administered to treat depression or anxiety. Excessive alcohol consumption has also been linked to erectile insufficiency. These forms of erectile insufficiency may be regarded as a subset of neurogenic or psychogenic insufficiency.

A number of methods to treat impotence are available. These treatments include pharmacological treatments, surgery and, in cases of psychogenic dysfunction, psychological counseling is sometimes effective. Psychogenic impotence often can be cured by counseling coupled with a demonstration to the patient that he is capable of having a full erection by inducing such an erection one of a few times in the patients. Insufficiency due to excessive alcohol consumption is sometimes cured by reducing or elimination such consumption.

In the rare cases, where the insufficiency is physical because of venous leakage, surgery can usually be employed to repair the venous lesion and thereby either cure the insufficiency or, if there remains an erectile insufficiency after repair of the venous lesion, render the insufficiency amenable to treatment by pharmacological methods. Also, penile implants, which provide a mechanical means to produce an erection sufficient for vaginal penetration, are widely used to treat impotence. In recent years, implants have been employed, especially in cases where pharmacological intervention is ineffective, which are usually cases of severe atherogenic impotence. Treatment of impotence with penile implants, however, entails serious disadvantages. Such

treatment requires surgery and necessitates total destruction of the erectile tissues of the penis, forever precluding normal erection.

Pharmacological methods of treatment are also available. Such methods, however, have not proven to be highly satisfactory and can be accompanied by severe side-effects. Papaverine is now widely used to treat impotence, although papaverine is ineffective in overcoming impotence due, at least in part, to severe atherosclerosis. Papaverine is effective in cases where the dysfunction is psychogenic or neurogenic and severe atherosclerosis is not involved. Injection of papaverine, a smooth muscle relaxant, or phenoxybenzamine, a non-specific blocker and hypotensive, into a corpus cavernosum has been found to cause an erection sufficient for vaginal penetration. Also, in cases where severe atherosclerosis is not a cause of the dysfunction, intracavernosal injection of phentolamine, an α -adrenergic blocker, causes an erection sufficient for vaginal penetration. The resulting erection is one of significantly shorter duration than that induced by intracavernosal injection of papaverine or phenoxybenzamine and is of such short duration that satisfactory sexual relations are difficult or impossible.

Treatment of impotence with papaverine or phenoxybenzamine often results in priapism, a locking-up of an erection for a long period of time, typically a few hours and sometimes longer than twenty-four hours. Priapism is a serious, deleterious side effect of treatment of erectile insufficiency with these drugs. Beyond the embarrassment that may be caused for some men, priapism is usually painful, irreversibly damages erectile tissue, and, to be relieved, requires bleeding or pharmacological intervention, such as injection of a sympathomimetic drug, such as adrenaline.

Even if priapism does not occur with use of papaverine, such use is associated with a painful, burning sensation in the first two or so minutes after the injection and there are indications that repeated use of papaverine causes undesirable, extensive intracavernous fibrosis. Further, as indicated above, impotence arising from severe atherosclerosis is not susceptible to treatment with papaverine, phenoxybenzamine, phentolamine or papaverine together with phentolamine. In any case,

phenoxybenzamine is not suitable for use in treating impotence because it is a carcinogen.

Thus, although impotence is a ubiquitous problem, there are few satisfactory methods available for treating this disorder. Because of the relatively invasive intervention involved and the high failure rate of penile prostheses, surgical approaches provide unattractive alternatives. A safe pharmacological approach to the treatment of impotence is still to be achieved.

What is needed is a pharmaceutical that is effective but lacking in significant side effects.

10 SUMMARY OF THE INVENTION

The present invention provides relates to methods for the treatment of sexual dysfunction in males and females (including but not limited to erectile dysfunction in males) in particular treatment groups. The methods of the present invention comprise the utilization of pharmaceutical compositions to patients who are free of symptoms of cardiac disease and who have not been treated with drugs which cause hypotensive effects, such as nitrites and nitrates. The compositions comprise quinolines and quinolones, including derivatives thereof.

It is not intended that the present invention be limited by the nature of the derivative. In one embodiment, the quinolone is an oxoquinoline. In yet another embodiment, the oxoquinoline is cilostazol (6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2(1H)-quinolinone; 6-[4-(1-cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydrocarbostyryl; 6-[4-(1-cyclohexyl-5-tetrazoyl)butoxy]-1,2,3,4-tetrahydro-2-oxoquinoline).

In yet other embodiments, metabolites of cilostazol are contemplated for use in the methods of the presently claimed invention. Metabolites of cilostazol include, but are not limited to monohydroxycilostazol, monohydroxydehydrocilostazol, 3,4-dihydro-6-hydroxy-2(1H)-quinolinone, their conjugates and dehydrocilostazol.

In one embodiment, the present invention contemplates halogenated quinolines (e.g., bromoquinoline) and isoquinolines (e.g., 1-methylisoquinoline and 5-

nitroisoquinoline). In another embodiment, the present invention contemplates halogenated quinolones (*e.g.*, flosequinolone). In a preferred embodiment, the quinolone is a thioquinolone or a sulphonyl or suphonyl derivatives thereof. In one embodiment, the halogenated quinolone is flosequinan (7-fluoro-1-methyl-3-methylsulphonyl-4-quinolone).

In one embodiment, the present invention contemplates a method, comprising:
a) providing: i) a male or female with symptoms of sexual dysfunction, and ii) flosequinan; and b) administering said flosequinan to said male or female. It is not intended that the present invention be limited to particular symptoms of sexual dysfunction. A variety of such symptoms are contemplated, including but not limited to, poor blood flow to the sexual organs and/or failure to achieve orgasm. In one embodiment, the present invention contemplates administering said flosequinan to said male or female under conditions such that blood flow to the sexual organs of said male or female is improved.

In another embodiment, the method comprises providing: i) a male or female with erectile dysfunction, and ii) flosequinan; and introducing said flosequinan to said female such that an erection (*i.e.* penile or clitoral) is produced.

It is not intended that the present invention be limited by the method of introduction of flosequinan. In one embodiment, the flosequinan is introduced into said male or female orally. In a preferred embodiment, the male or female is an adult human and the oral dosage is in a single dose per day of up to approximately 100 milligrams, and more preferably, between approximately fifty to approximately seventy-five milligrams. In other embodiments said flosequinan is introduced cutaneously, transurethrally, or by standard injection.

In one embodiment, the method comprises a) providing: i) a patient (whether male or female) suffering from symptoms of sexual dysfunction who is free from cardiac disease; and ii) flosequinan; and b) introducing said flosequinan to said patient such that such symptoms are reduced.

In another embodiment, the method comprises a) providing: i) a patient (whether male or female) suffering from symptoms of sexual dysfunction who is not

being treated (and/or has not been treated in the past) with a drug that causes hypotensive effects, and ii) flosequinan; and b) introducing said flosequinan to said patient such that such symptoms are reduced.

5 In another embodiment, the method comprises a) providing: i) a patient (whether male or female) suffering from symptoms of sexual dysfunction who is not being treated (and/or has not been treated in the past) with a nitrite or nitrate, and ii) flosequinan; and b) introducing said flosequinan to said patient such that such symptoms are reduced.

10 The present invention is not limited by the degree of response by the subject. In one embodiment, the male erection induced is sufficient for vaginal penetration.

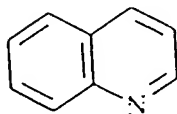
Likewise, the present invention also contemplates the use of sexual stimulation in addition to the application of a pharmaceutical composition. For example, one embodiment comprises a) providing: i) a male, having a penis, with erectile dysfunction, and ii) flosequinan, iii) sexual stimulation; and b) introducing said
15 flosequinan and sexual stimulation to said male such that an erection is produced.

Likewise, the present invention is not limited by the nature of the sexual stimulation. In one embodiment, the sexual stimulation is sexually explicit media. In another embodiment, the sexual stimulation involves manipulation of the penis, such as with vibration.

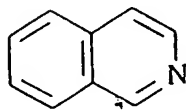
20 It is not intended that the present invention be limited by the nature of the formulation. In one embodiment, the present invention contemplates a formulation comprising a quinoline or derivative thereof in a mixture comprising lactose.

DEFINITIONS

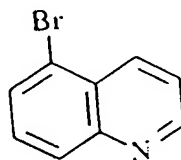
As used herein, the term "quinoline" refers to chemical compositions comprising quinoline as set forth in the following structure:



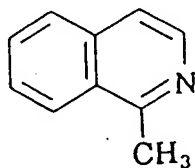
as well as other forms of quinoline, (*e.g.*, isoquinoline):



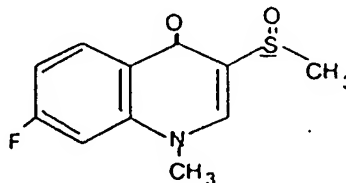
- 5 As used herein, the phrase "derivatives of quinoline" refers to chemical compositions comprising quinoline with a chemical group attached, including halogenated quinoline, *e.g.*, 5-bromoquinoline:



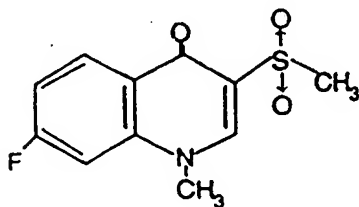
and 1-methylisoquinoline:



As used herein, the phrase "methysulphanyl derivatives of quinoline" refers to chemical compositions comprising quinoline with a methysulphanyl group attached. Examples include flosequinan (7-fluoro-1-methyl-3-methysulphanyl-4-quinolone):



and sulfone metabolites of flosequinan:



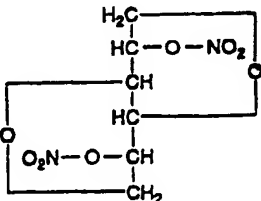
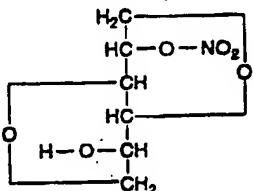
5 As used herein, a patient who is "free from cardiac disease" and a patient who is "free from symptoms of cardiac disease" indicate that the patient has not been diagnosed with angina, myocardial infarction, congestive heart failure and that symptoms of angina, ischemia, myocardial infarction, congestive heart failure have not been detected, respectively.

10 As used herein, "drugs that have hypotensive effects" are those drugs which, when administered, cause the patient's end-diastolic blood pressure to be reduced. Nitrates are commonly used drugs which have hypotensive effects.

 As used herein, "nitrates" are compounds that contain the $-\text{NO}_3$ - moiety. Nitrates typically used in the clinic are shown in Table 1.

15 As used herein, "nitrites" are compounds that contain the $-\text{NO}_2$ - moiety. Nitrites typically used in the clinic are shown in Table 1.

TABLE 1

NONPROPRIETARY NAMES AND TRADE NAMES	CHEMICAL STRUCTURE	PREPARATIONS, USUAL DOSES, AND ROUTES OF ADMINISTRATION*
Amyl nitrite (isoamyl nitrite)	$\begin{array}{c} \text{H}_3\text{C} \\ \diagup \\ \text{CHCH}_2\text{CH}_2\text{ONO} \\ \diagdown \\ \text{H}_3\text{C} \end{array}$	Inh: 0.18 or 0.3 ml, inhalation
Nitroglycerin (glyceryl trinitrate; NITRO-BID, NITROSTAT, NITROL, NITRO-DUR, others)	$\begin{array}{c} \text{H}_2\text{C}-\text{O}-\text{NO}_2 \\ \\ \text{HC}-\text{O}-\text{NO}_2 \\ \\ \text{H}_2\text{C}-\text{O}-\text{NO}_2 \end{array}$	T: 0.15 to 0.6 mg as needed S: 0.4 mg per spray as needed C: 2.5 to 9 mg two to four times daily B: 1 mg every 3 to 5 h O: 1.25 to 5 cm ($\frac{1}{2}$ to 2 in.), topically to skin every 4 to 8 h D: 1 disc (2.5 to 15 mg) every 24 h IV: 5 $\mu\text{g}/\text{min}$; increments of 5 $\mu\text{g}/\text{min}$
Isosorbide dinitrate (ISORDIL, SORBITRATE, DILATRATE, others)		T: 2.5 to 10 mg every 2 to 3 h T(C): 5 to 10 mg every 2 to 3 h T(O): 10 to 40 mg every 6 h C: 40 to 80 mg every 8 to 12 h
Isosorbide-5-mononitrate (IMDUR, ISMO, others)		T: 10 to 40 mg twice daily C: 60 mg daily
Erythritol tetranitrate (CARDILATE)	$\begin{array}{c} \text{H}_2\text{C}-\text{O}-\text{NO}_2 \\ \\ \text{HC}-\text{O}-\text{NO}_2 \\ \\ \text{HC}-\text{O}-\text{NO}_2 \\ \\ \text{H}_2\text{C}-\text{O}-\text{NO}_2 \end{array}$	T: 5 to 10 mg as needed T(O): 10 mg three times daily

* B buccal (transmucosal) tablet; C, sustained-release capsule or tablet; D, transdermal disc; Inh, inhalant; IV, intravenous injection; O, ointment; S, lingual spray; T, tablet for sublingual use; T(C), chewable tablet; T(O), oral tablet or capsule.

As used herein, the term "erectile dysfunction" refers to certain disorders of the cavernous tissue of the penis and the associated fascia which produce impotence, the inability to attain a sexually functional erection;

5 As used herein "standard injection" refers to the placement of a pharmaceutical composition into a subject (*e.g.*, with a hypodermic needle). For example, such injection can be made subcutaneously, intravenously, intramuscularly, intracavernosally, *etc.*

As used herein, "intracavernosal" injection is injection into the corpus cavernosum of the penis.

10 As used herein, an "erection" refers to the condition of a penis whereby it is at least semi-rigid as opposed to being in a flaccid state.

As used herein, "by oral administration" refers to the introduction of a pharmaceutical composition into a subject by way of the oral cavity (*e.g.*, in aqueous liquid or solid form).

15 As used herein, "cutaneously" refers to the introduction of a pharmaceutical composition into a subject by application to the surface of the skin such that the composition is absorbed into the subject.

As used herein, "transurethrally" refers to the introduction of a pharmaceutical composition to the urethra of a subject such that the composition is absorbed into the subject.

20 As used herein, "intranasally" refers to the introduction of a pharmaceutical composition within the nasal cavity.

As used herein, "respiratory inhalation" refers to the introduction of a pharmaceutical composition within the respiratory tract.

25 As used herein, "sufficient for vaginal penetration" refers to the state of an erection such that the penis is capable of entering a vagina without manual manipulation.

As used herein, "sexual stimulation" refers to activity that would induce an erection in a male without erectile dysfunction (*e.g.*, sexually explicit media, manual manipulation, vibration, live erotic entertainment, *etc.*)

As used herein, "sexually explicit media" refers to films, videos, books,
5 magazines, *etc.* that depict sexual activity.

As used herein "single dosage" refers to a pharmaceutical composition of a formulation that is capable of achieving its intended effect in a single application.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides relates to methods for the treatment of sexual
10 dysfunction in males and females (including but not limited to erectile dysfunction in males) in particular treatment groups. The methods of the present invention comprise the utilization of pharmaceutical compositions to patients who are free of symptoms of cardiac disease and who have not been treated with drugs which cause hypotensive effects, such as nitrites and nitrates. The compositions comprise quinolines and
15 quinolones, including derivatives thereof.

In one embodiment flosequinan is administered. Importantly, flosequinan may potentiate the hypotensive effects of nitrates, and its administration to patients who are concurrently using organic nitrates in any form may be contraindicated.

In one embodiment, the present invention contemplates the use of compositions
20 that are effective to induce an erection in a human male suffering from impotence of any origin, other than anatomical deficiencies (*i.e.*, lacking a penis or a significant portion thereof) that preclude an erection sufficient for vaginal penetration. In particular, these compositions may be used to induce an erection in a male suffering from impotence caused by severe atherosclerosis, and also impotence that is
25 neurogenic or psychogenic in origin. The compositions utilized in the methods of the present invention comprise quinolines and quinolones, including derivatives thereof.

While the present invention is not limited by the nature of the derivatives, in one embodiment, the present invention encompasses the use of a variety of quinoline

derivatives (e.g., 5-bromoquinoline, 5-nitroisoquinoline, 8-nitroisoquinoline and 1-methylisoquinoline). One skilled in the art can readily produce such derivatives as set forth in McMurry, Organic Chemistry, 2nd Ed., Brooks/Cole Publishing, Belmont, CA (1988), pages 1044-1045 and 1076.

5 In another embodiment, the present invention contemplates the use of methylthio and methylsulphinyl derivatives of quinoline. In a preferred embodiment, the methylsulphinyl derivative is flosequinan (7-fluoro-1-methyl-3-methylsulphinyl-4-quinolone).

10 Methods of producing methylsulphinyl and methylthio derivatives of quinoline, including flosequinan, are set forth in U.S. Patent Nos. 5,079,264 and 5,011,931 to MacLean *et al.*, hereby incorporated by reference. While it is not necessary to understand any particular mechanism to carry out the present invention, it is believed that in some circumstances flosequinan can act as a direct-acting vasodilator to relax the corpus cavernosum smooth muscle cells, which in turn increases blood flow into
15 the cavernosa space. This then leads to increased cavernosa pressure to produce an erect penis.

The action of flosequinan in the body is not precisely understood. Its activity in the body is attributed to flosequinan itself, as well as its sulfone metabolite. It has been reported to be useful to some degree in the treatment of heart failure. [See Kelso
20 *et al.*, *J. Cardiovasc. Pharmacol.* 25:376 (1995)]. However, its action appears to have little effect in patients with end-stage failure [Perreault *et al.*, *Br. J. Pharmacol.* 106:511 (1992)] and does not affect mortality or arrhythmias following coronary artery ligation [Jones *et al.*, *Br. J. Pharmacol.* 108:1111 (1993)].

Likewise, flosequinan has been reported to be a selective inhibitor of
25 phosphodiesterase III [Gristwood *et al.*, *Br. J. Pharmacol.* 105:985 (1992)]. [Frodsham *et al.*, *Eur. J. Pharmacol.* 211:383 (1992)], however, report that the phosphodiesterase inhibition of flosequinan, as relevant to its efficacy in heart failure, is questionable. Thus, the application of flosequinan to particular purposes in the body is not well-characterized and must be determined empirically.

DIAGNOSIS OF MALE ERECTILE DYSFUNCTION

Determination whether a human male is suffering from impotence that is substantially only neurogenic or psychogenic is readily made by a person skilled in the art using a number of readily available diagnostic procedures. Thus, a male suffering from impotence can first be given a physical examination with particular attention to possible penile and scrotal pathology, whereby any anatomical deficiency precluding an erection sufficient for vaginal penetration can be detected. In the absence of such an anatomical deficiency, the male can be subjected to tests, whereby penile venous leakage or severe or untreatable atherosclerosis can be detected.

Such tests include determination of the penobrachial blood pressure index (PBPI), doppler investigation of the penile arteries, and a papaverine test. The PBPI is the penile systolic blood pressure divided by the systolic blood pressure determined at one of the arms. These blood pressures can be determined by any number of standard techniques. Thus, the penile systolic blood pressure can be determined by i) placing an inflatable cuff around the base of the free part of the penis in the flaccid state which is capable of being used to apply variable pressure, readable from a gauge, to an object around which the cuff is placed, ii) localizing the penile arteries with a Doppler ultrasound probe (*e.g.*, 8 MHz probe, such as the Mini Doplex D500 available from Huntleigh Technology, Luton, United Kingdom), and then iii) inflating and deflating the cuff and ascertaining the pressure at which the Doppler sound reappears.

The pressure at which the Doppler sound reappears is the penile systolic blood pressure. A male's penile blood pressure is regarded as normal if his PBPI is >0.80 . With regard to Doppler investigation, each of the two penile cavernous arteries is investigated distal to the aforementioned cuff using the Doppler ultrasound problem. The function of each of the two arteries is assessed by Doppler ultrasound using an arbitrary scale of 0, 1, 2 or 3, where 0 means that the function is so deficient that the artery cannot be located and 3 means that the artery is well enough that maximal Doppler sound is observed.

In the papaverine test, a tourniquet is placed at the base of the free part of the penis and tightened and then, with the patient seated, 30 mg of papaverine in 1 ml of a

physiologically acceptable fluid (e.g., physiological saline or phosphate-buffered saline) is injected into the penile cavernous body. In persons suspected of having impotence due to a suprasacral nerve lesion or a psychogenic dysfunction, only 15 mg of papaverine is administered, because of the high incidence of papaverine-induced priapism in such cases.

Five minutes after the injection, the tourniquet is removed and an ultrasound Doppler investigation of the penile cavernous arteries is carried out as described above. The function of the arteries is regarded as normal if both of them score a 3 on the arbitrary scale. After the Doppler investigation, penile vibration, at about a 4 Hz with an amplitude of about 1.2 mm (carried out with, e.g., a Vibrector, from Multicept, Gentofte, Denmark) is carried out for five to ten minutes and then erectile response is evaluated.

Erectile response is classified as full rigidity, if the angle between the penis and the legs in the standing position is $>90^\circ$, and tumescence or no response if the angle is less than or equal to 45° . An impotent male, who does not have an anatomical deficiency that would preclude having an erection sufficient for vaginal penetration, who has a PBPI >0.80 , who has scores of 2 or 3 in Doppler ultrasound investigations of both of the cavernous arteries of the penis, after papaverine injection as described above, and who has a fully rigid erection after papaverine injection and vibration as described above, is suffering from impotence that is "substantially only neurogenic or psychogenic" in origin.

It is possible that atherosclerosis or venous leakage contributes to such impotence, and atherosclerosis likely does contribute if the score is less than 3 in the Doppler investigation of one or both of the cavernous arteries after papaverine injection; but any venous leakage or atherosclerosis in such impotence is not untreatable and, consequently, is not a substantial factor in the impotence and such atherosclerosis, if any, is less than severe.

Impotence, which is a side-effect of drugs such as beta-blockers, is deemed to be neurogenic impotence in the present specification. Similarly, impotence which is a result of alcoholism or excessive consumption of alcohol, is deemed to be neurogenic

or psychogenic impotence, for purposes of the present specification. Thus, a male who is diagnosed in accordance with the present specification as suffering from impotence that is "substantially only neurogenic or psychogenic" in origin is suffering from impotence that is substantially only neurogenic, psychogenic or neurogenic and psychogenic in origin, even though an underlying cause of the impotence has been identified as a side-effect of a drug, alcoholism or excessive consumption of alcohol.

Generally, a male with a PBPI less than about 0.60, with scores of 0 in Doppler investigations of both penile cavernous arteries (after papaverine injection as described above), and with a less than fully rigid erection after papaverine injection and vibration will have impotence caused by "untreatable" atherosclerosis. Methods are available to ascertain whether impotence is untreatable because of venous leakage.

One method of ascertaining whether untreatable venous leakage is a cause of impotence is by cavernosometry, optionally supplemented with cavernosography. [See, e.g., Delcour *et al.*, *Radiology* 161:799 (1986); Porst *et al.*, *J. Urol.* 137:1163 (1987); Lue *et al.*, *J. Urol.* 37:829 (1987)]. Cavernosometry can be done using, both before and after intracavernosal injection of 60 mg of papaverine (in 1 ml of physiological saline), infusion of physiological saline through a 19-gauge needle into one corpus cavernosum with a 21-gauge needle inserted into the other corpus cavernosum for measurement of intracorporal pressure (which is recorded on a plotter).

The infusion rates needed to induce and maintain an erection are measured. If the infusion rate needed to maintain an erection is greater than 50 ml/min before administration of the papaverine and greater than 15 ml/min after administration of the papaverine, untreatable venous leakage is present. As long as an erection can be achieved at some flow rate less than about 100 ml/min before injection of the papaverine and less than about 50 ml/min after the injection of papaverine, it might be possible, using cavernosography, to locate the venous lesion associated with the leakage, and thereby confirm the diagnosis based on cavernosometry and provide information for possible surgical correction for the leakage. In the cavernosography, the penis is X-rayed, both before and after intracavernosal injection of 60 mg papaverine (in 1 ml of physiological saline), while infusing contrast medium into the

corpus cavernosum (e.g., through a 19-gauge needle) at a flow rate that maintains an erection during the x-raying. Numerous contrast media suitable for the procedure are available in the art; these are typically aqueous solutions of iodinated compounds that provide between about 180 mg/ml and about 360 mg/ml of iodine. Examples are a solution of iohexol providing 240 mg/ml of iodine sold by Winthrop Pharmaceuticals, New York, N.Y., USA, and a solution of iopamidol providing 300 mg/ml iodine sold by Astra Meditec, Goteborg, Sweden. Typically 50-100 ml of the contrast medium will be employed for each x-ray (i.e., before and then after the injection of papaverine). In the cavernosometry and cavernosography, 30 mg papaverine (in 1 ml physiological saline) coupled with stimulation by vibration can be employed in place of 60 mg papaverine (in 1 ml physiological saline).

DIAGNOSIS OF FEMALE ERECTILE DYSFUNCTION

Females have sexual dysfunction. Post-menopausal women often complain of discomfort with intercourse, dryness of the vagina and diminished vaginal arousal. Studies comparing sexual dysfunction in couples have revealed 40% of the men had erectile or ejaculatory dysfunction whereas 63% of the women had arousal or orgasmic dysfunctions. Similar to male sexual dysfunction, the prevalence of female sexual dysfunction has been shown to increase with age and be associated with the presence of vascular risk factors and the development of the menopause.

The clitoris is the homologue of the penis. It is a cylindrical, erectile organ composed of the glans, corporal body and the crura. The corporal body is surrounded by a fibrous sheath, tunica albuginea, which encases cavernosal tissue consisting of sinusoids and surrounding smooth muscle. The clitoris responds to sexual excitement by tumescence and erection, although this does not occur with the degree of pressure elevation as found during penile erection. The characteristics of the clitoral blood flow, however, approximately parallel those of the male. See K. Park *et al.*, "Vasculogenic female sexual dysfunction: The hemodynamic basis for vaginal engorgement insufficiency and clitoral erectile insufficiency," *Int. J. Impotence Res.* 9:27 (1997).

Post-menopausal women and women with a history of vascular risk factors have been shown to have significantly more complaints of self-reported female vaginal and clitoral dysfunctions than pre-menopausal women or women without vascular risk factors. Such problems include, but are not limited to, athereosclerosis-induced vaginal engorgement insufficiency and clitoral erectile insufficiency syndromes.

Determination whether a human female is suffering from poor blood flow or supply is readily made by a person skilled in the art using a number of readily available diagnostic procedures. The human vagina receives arterial blood supply from the vaginal artery, the vaginal branch of the uterine artery, the internal pudendal artery, and the vaginal branches of the middle rectal artery. Blood flow in these areas can readily be assessed by a number of techniques. Arterial blood can be obtained and the blood levels of cholesterol and triglycerides can be analyzed as a first step. However, the preferred method is imaging.

While relatively non-invasive imaging is preferred, more invasive techniques can be used. For example, vaginal wall blood flow can be measured by laser Doppler flow probes placed into the vaginal muscularis layer within the spongy region of blood-filled spaces and vascular smooth muscle. Clitoral intracavernosal erectile tissue blood flow can be measured with a similar laser Doppler flow probe placed into the corporal bodies. The flow probes are connected to a laser Doppler flowmeter (Transonic Systems, Inc.) which is calibrated against an internal standard reading flow in units of ml/min/100 gm of tissue.

The laser Doppler probe uses the Doppler shift of a projected beam of laser light that registers on a photodetector. Static tissues will produce no Doppler shift in wavelength but moving red blood cells will produce a shift proportional to the red cell velocity.

TREATMENT OF MALE AND FEMALE ERECTILE DYSFUNCTION

It is not intended that the present invention be limited by the particular nature of the therapeutic preparation. For example, the quinolines or quinolone derivatives (e.g., flosequinan) can be provided together with physiologically tolerable liquid, gel or solid carriers, diluents, adjuvants and excipients. In addition, quinoline or quinolone analogs may be used together with other chemotherapeutic agents. On the other hand, formulations may also contain such normally employed additives as binders, fillers, carriers, preservatives, stabilizing agents, emulsifiers, buffers and excipients as, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, cellulose, magnesium carbonate, and the like. These compositions typically contain 1%-95% of active ingredient, preferably 2%-70%.

The present invention is not limited by the method of introduction of the therapeutic compound to the body. Among other methods, the present invention contemplates administering cutaneously, orally, intracavernosally, transurethraly or by standard injection.

The present invention also contemplates administering flosequinan to the patient intranasally or through respiratory inhalation. Formulations suitable for intranasal administration include ointments, creams, lotions, pastes, gels, sprays, aerosols, oils and other pharmaceutical carriers which accomplish direct contact between flosequinan or a pharmaceutical composition comprising flosequinan and the nasal cavity. Examples of pharmaceutical compositions administered intranasally are described in U.S. Patents 5,393,773 and 5,554,639 to Craig *et al.*; and 5,801,161 to Merkus, all hereby incorporated by reference. Formulations suitable for respiratory inhalation include ointments, creams, lotions, pastes, gels, sprays, aerosols, oils and other pharmaceutical carriers which accomplish direct contact between flosequinan or a pharmaceutical composition comprising flosequinan and the respiratory tract. Examples of pharmaceutical compositions administered through respiratory inhalation are described in U.S. Patent 4,552,891 to Hu *et al.*; 5,869,479 to Kreutner *et al.*, and 5,864,037 to Chasis *et al.*, all hereby incorporated by reference.

In some embodiments, intranasal administration and respiratory inhalation are the preferred modes of administration due to the ease of administration and faster onset of therapeutic activity. It is contemplated that intranasal administration and respiratory inhalation are advantageous as they may allow a smaller effective dosage to be administered than would be possible with the oral route of administration. A preferred mode of administration comprises administration to the lung. Intrapulmonary delivery of pharmacologic agents to patients can be accomplished via aerosolization. Alternatively, the agent may be administered to the lung through a bronchoscope. Of course, the therapeutic agents may be investigated for their efficacy via other routes of administration, including parenteral administration.

Oral administration of flosequinan is effective, with a mean absolute bioavailability of 72% following a single dose of fifty milligrams. Peak plasma concentrations of flosequinan are observed 1-2 hours following oral administration, while peak metabolite plasma levels are observed about seven hours following oral dosage. While the present invention is not limited to a specific dosage level, for adult humans, in one embodiment the dosage is a single dosage per day of 50 milligrams, while in another embodiment the dosage is a single dosage per day of 75 milligrams.

Flosequinan is water soluble and is soluble in many organic solvents. Thus, while the present invention is not limited by the form of oral administration, aqueous and organic solution of flosequinan for oral administration is contemplated. Likewise, flosequinan can be associated with a solid pharmaceutical carrier for solid oral administration (*i.e.*, in pill form). One skilled in the art is able to readily prepare such solid formulations, and in one embodiment, the inactive ingredients include croscarmellose sodium, hydroxypropyl methylcellulose, lactose, magnesium stearate, methocel E5, microcrystalline cellulose, povidone, propylene glycol and titanium dioxide.

Flosequinan may also be administered cutaneously in a carrier adapted for topical administration. Such carriers include creams, ointments, lotions, pastes, jellies, sprays, aerosols, bath oils, or other pharmaceutical carriers which accomplish direct contact between flosequinan and the pore of the skin. In general pharmaceutical

preparations may comprise from about 0.001% to about 10%, and preferably from about 0.01 to 5% by w/w of the active compound (e.g., flosequinan) in a suitable carrier. In some cases it may be necessary to dissolve the flosequinan in an appropriate solvent such as ethanol or DMSO (dimethylsulfoxide), and the like, to facilitate incorporation into a pharmaceutical preparation. Likewise, the present invention can be incorporated in other products associated with sexual activity. For example, a coated, erection inducing condom as disclosed in U.S. Pat. No. 4,829,991, hereby incorporated by reference, and can be utilized with flosequinan or flosequinan in a pharmaceutical carrier as described above.

While the present invention is not limited by a specific method of introducing flosequinan intracavernosally, injection of flosequinan can be carried out by any conventional injection means (e.g., employing an hypodermic syringe and needle or a similar device such as the NovolinPen. sold by Squibb-Novco, Inc., Princeton, N.J., USA). This injection may be by subject injecting himself or by another person (such as a partner during sexual relations or a physician prior to sexual relations) injecting the male whose erection is to be induced. Methods for intracavernosal injection are described in U.S. Patent No. 5,447,912 to Gerstenberg *et al.*, hereby incorporated by reference.

Flosequinan can be introduced intracavernosally in a physiologically acceptable composition. Such compositions are aqueous solutions that are physiologically acceptable for administration by intracavernosal injection into the penis. The physiologically acceptable carrier is selected such that it is not painful or irritating upon intracavernosal injection. The physiologically acceptable compositions will preferably be sterile at the time of administration by intracavernosal injection.

Among the physiologically acceptable compositions for use in the methods is physiological saline or phosphate buffered saline, in which flosequinan is dissolved or suspended, such that the resulting composition is suitable for intracavernosal injection. Such a physiologically acceptable composition can also include a non-irritant preservative, such as, e.g., benzalkonium chloride at 0.05% (w/v) to 0.2% (w/v). As the skilled artisan will understand, there are numerous non-toxic salts of VIP, PHM

and α -adrenergic blockers that can be employed in a physiologically acceptable composition for use in the methods herein, including, among others, the chloride, bromide, acetate, sulfate, and mesylate salts.

5 In carrying out the methods, it is preferred that, for a period of time between about 1 minute and about 15 minutes (preferably about 5 minutes-10 minutes), the penis is constricted near the base thereof and between the base and the point at which the injection into a corpus cavernosum occurs, in order to limit loss of injected fluid from the corpus cavernosum before the ingredients in the fluid, that are active in inducing erection, have been able to have erection-inducing effects. The constriction
10 can be effected by any means known in the art, such as with a tourniquet, cuff, rubber band or the like, or even manually, in order to slow the release of the injected fluid and the pharmacologically active substance(s) therein into the general circulation.

Likewise, the present invention is not limited by a particular method for introducing flosequinan transurethrally. In one embodiment, flosequinan is introduced
15 to the urethra in a carrier as described for cutaneous administration. Devices and methods for transurethral introduction of pharmaceutical compositions is described in U.S. Patent No. 5,474,535 to Place *et al.*; Voss, U.S. Pat. No. 4,801,587 and Kock, EPA 0357581, all hereby incorporated by reference.

Additional methods of introducing flosequinan transurethrally include the use of
20 medicated catheters, such as those used to prevent or treat localized infections and irritation of the urethra and bladder (*See* U.S. Pat. No. 4,640,912, hereby incorporated by reference). Alternatively, transurethral administration of pharmaceutical compositions is presented in U.S. Pat. Nos. 4,478,822, 4,610,868, 4,640,912 and 4,746,508, all hereby incorporated by reference, and medicated urethral suppositories,
25 inserts or plugs, typically containing anti-infective agents or spermicide are disclosed in U.S. Pat. Nos. 1,897,423, 2,584,166, 2,696,209 and 3,373,746, all incorporated by reference.

While the present invention is not limited to the method of injecting flosequinan, in the preferred embodiment, it is injected with a standard syringe. One

skilled in the art would be capable of injecting flosequinan with a carrier as described for intracavernosal injection.

In one embodiment, the administration of the compositions of the present invention is accompanied by sexual stimulation to induce an erection. The sexual stimulation can begin before or after the introduction of flosequinan. If the stimulation begins after the injection, it is preferably begun within 5 to 10 minutes to insure that there is significant overlap of the pharmacological effects of the pharmaceutical composition administered and the stimulative effects of the sexual stimulation. Whether the stimulation begins before or after the injection, it will continue preferably at least until an erection sufficient for vaginal penetration is achieved.

Sexual stimulation as prescribed by these methods, includes any form of sexual stimulation that would induce an erection in a normal male who is not suffering from erectile insufficiency. The sexual stimulation can be that which occurs in the course of sexual relations between the subject and another person or can be outside sexual relations with another person. Examples of methods of sexual stimulation include, alone or in combination, touching or erotically manipulating erogenous areas of the genital organs or other erogenous parts of the body; providing visual stimulation, as with a sexually explicit media (*e.g.*, pornographic film) or other form of sexually stimulative show or display. Additionally, providing vibratory stimulation to the penis, at between about 30 Hz and about 100 Hz with an amplitude of about 1 mm to about 5 mm, as can be provided, for example, by resting the penis on the table of a vibrating apparatus such as that of a Vibrector system (Multicept, Genofte, Denmark).

In inducing an erection in an impotent male outside of sexual relations, as, for example, when a physician induces an erection in a patient suffering from psychogenic impotence, a preferred method of sexual stimulation includes providing visual stimulation, as with a pornographic film, simultaneously with vibratory stimulation of the penis, as with a Vibrector system set to between about 30 Hz and about 60 Hz (usually about 50 Hz) in frequency and between about 1 mm and about 2.5 mm (usually about 2.2 mm) in amplitude.

From the above, it should be clear that the present invention provides methods of treatment of male erectile dysfunction with pharmaceutical agents. In particular, quinolines and quinolones are administered therapeutically to patients having such dysfunction.

CLAIMS

We claim:

1. A method, comprising:
 - a) providing:
 - 5 i) a subject diagnosed with erectile dysfunction, and
 - ii) a therapeutic formulation comprising a quinoline; and
 - b) introducing said formulation to said subject such that an erection is produced.
2. The method of Claim 1, wherein said quinoline is an oxoquinoline.
- 10 3. The method of Claim 1, wherein said quinoline is a halogenated quinoline.
4. The method of Claim 3, wherein said halogenated quinoline is flosequinan.
5. The method of Claim 4, wherein said flosequinan is introduced into said
15 subject by oral administration.
6. The method of Claim 5, wherein said subject is an adult human and said oral administration comprises up to approximately 100 milligrams of flosequinan.
7. The method of Claim 4, wherein said flosequinan is introduced into said subject cutaneously.
- 20 8. The method of Claim 4, wherein said flosequinan is introduced into said subject transurethrally.

9. The method of Claim 4, wherein said flosequinan is introduced into said subject intracavernosally.

10. The method of Claim 1, wherein said subject is free from cardiac disease.

5 11. The method of Claim 1, wherein said subject is a male.

12. The method of Claim 1, wherein said subject is a female.

13. The method of Claim 1, wherein said subject is not being treated with a drug that causes hypotensive effects.

10 14. The method of Claim 1, wherein said subject has not been treated in the past with a drug that causes hypotensive effects.

15. The method of Claim 1, wherein said subject is not being treated with a nitrite or nitrate.

15 16. The method of Claim 15, wherein said nitrate is selected from the group consisting of glyceryl trinitrate, isosorbide dinitrate, isosorbide-5-mononitrate and erythrityl tetranitrate.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/09610

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61F 2/02, 13/02; A61K 9/20, 9/48

US CL : 424/423, 434, 451, 464

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/423

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,492,911 A (STIEF) 20 February 1996, see entire document.	1-16

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

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Date of mailing of the international search report

24 JUN 1999

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